Review

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Metformin acts on the gut-brain axis to ameliorate antipsychotic-induced metabolic dysfunction

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SUMMARY Antipsychotic-induced metabolic dysfunction (AIMD) is an intractable clinical challenge worldwide. The situation is becoming more critical as second-generation antipsychotics (SGAs), to a great extent, have replaced the role of first-generation antipsychotics in managing major psychiatric disorders. Although the exact mechanisms for developing AIMD is intricate, emerging evidence has indicated the involvement of the microbiota-gut-brain axis in AIMD. SGAs treatment may change the diversity and compositions of intestinal flora (*e.g.*, decreased abundance of *Bacteroidetes* and *Akkermansia muciniphila*, and increased *Firmicutes*). Short-chain fatty acids and other metabolites derived from gut microbiota, on the one hand, can regulate the activity of intestinal endocrine cells and their secretion of satiety hormones (*e.g.*, glucagon-like peptide 1, peptide YY, cholecystokinin and ghrelin); on the other hand, can activate the vagus nerve or transport into the brain to exert a central modulation of foraging behaviors via binding to neuropeptide receptors. Interestingly, metformin, a classical antidiabetic agent, is capable of alleviating AIMD possibly by regulating the microbiota-gut-brain axis. That is, metformin can not only partially reverse the alterations of gut microbial communities due to SGAs treatment, but also play a positive role in rectifying the disturbances of peripheral and central satiety-related neuropeptides. Current evidence has indicated a promising role for metformin on ameliorating AMID, but further verifications in well-designed clinical trials are still warranted.

Keywords antipsychotic-induced metabolic dysfunction, gut-brain axis, gut microbiota, metformin, hypothalamus, neuropeptide

1. Introduction

In recent decades, second-generation antipsychotics (SGAs) have gradually replaced classic antipsychotics as the first-line choice for treatment of psychotics and related disorders due to their favorable therapeutic outcomes, fewer extrapyramidal events, and lower recurrence rate (*1*). However, many animal and human studies have found that taking SGAs (especially olanzapine [OLZ] and risperidone [RIS]) can cause significant weight gain and metabolic dysfunction (*2,3*). The longer the drug is taken, the more severe the metabolic side effect seems to be (*3,4*), and first-time users of SGAs are more likely to gain weight (*5*). Antipsychotic-induced metabolic dysfunction (AIMD), such as obesity and insulin resistance, also leads to decreased treatment compliance, which makes the treatment more difficult and increases treatment cost. Clinical studies have shown that metformin combined with SGAs can effectively ameliorate AIMD (*6*), but its mechanism is not fully elucidated. Interestingly, consumption of non-antibiotics, such as antidiabetics (metformin) and SGAs, has been associated with alterations in gut microbiome composition, which may be attributed to their antibiotic-like effects (*7*). Joint actions of metformin and antipsychotics not only can affect the composition and metabolism of intestinal microbes, but also modulate the expression of neuropeptides and neurotransmitter receptors in the brain, which may help to alleviate AIMD. In this

review, we discuss the AIMD induced by SGAs, its relationship with the microbiota-gut-brain axis, and the potential mechanisms of metformin in alleviating AIMD *via* the gut-brain axis.

2. Second-generation antipsychotic-induced metabolic disorder

Antipsychotic drugs are mainly used in managing mental disorders with psychotic symptoms, such as schizophrenia, schizoaffective psychosis and mania. According to the time sequence of their emergence and pharmacological characteristics, antipsychotics are mainly classified into two categories, SGAs and first-generation antipsychotics (FGAs). The former gradually replaces FGAs because of their less extrapyramidal adverse effects within the treatment dosage. SGAs exert antipsychotic effects predominately by blocking dopamine 2 (D_2) receptor and 5-hydroxytryptamine 2A ($5\text{-}HT_{2A}$) receptor. However, accumulating studies have indicated that patients receiving antipsychotic treatment encountered an increased risk of developing metabolic abnormalities (such as weight gain and type 2 diabetes) (*2*). Albeit following a short treatment period (≤ 6 weeks), the weight of patients receiving antipsychotics for the first time increased significantly (*5*). In this study, the average weight gain of OLZ, quetiapine and RIS treatment was 3.42 kg, 1.91 kg and 2.68 kg, respectively (*5*). Based on an integrated clinical trial database, a study compared short-term (4-12 weeks, N = 1,742) versus long-term (1 year, N = 1,649) effects of different antipsychotics on patient weight within a standard treatment dose, and found significant differences among different SGAs (*3*). Compared to placebo, patients receiving OLZ or RIS had a greater incidence of weight gain, but not in those with haloperidol or ziprasidone treatment (3). Median weight increase per month was similar for the short-term and long-term exposure cohorts (*3*). Another meta-analysis including 11 studies also investigated the difference of short-term and long-term antipsychotic treatment on weight gain (*4*). In this study, drug-free patients were chosen for comparison, and antipsychotic drug exposure duration was selected for three periods (4-8 weeks, 10-12 weeks, and 24-48 weeks). Compared to short-term intervention, long-term consumption of antipsychotic drugs could result in more apparent weight gain (*4*). A more recent meta-analysis of 150 double-blind studies found that OLZ, chlorine azepine, amisulpride, and RIS were superior to FGAs in overall efficacy, and patients taking OLZ and RIS had a lower probability of recurrence than those taking FGAs. The incidence of extrapyramidal effects caused by SGAs was also lower than haloperidol, a classic FGA. However, compared with haloperidol, the weight gain effects of OLZ, clozapine, amisulpride, RIS, and quetiapine were apparently more significant (*8*). Similar findings were shown in other studies that clozapine and OLZ had the highest risk of weight gain, and other drugs (*e.g.*, RIS, quetiapine, and amisulpride) had a relatively low or moderate risk, while ziprasidone and aripiprazole (ARI) showed lowest risk (*9*). Interestingly, compared to those who were in a chronic course, patients diagnosed with first-episode psychotic disorder (FEP) were more likely to have weight gain (*10*). Taken together, these findings reveal that AIMD is a highly prevalent and inevitable clinical challenge. Although the mechanisms underlying AIMD were not fully understood, recently more and more pieces of evidence have suggested that AIMD may be closely related to the gut-brain axis.

3. Metabolism and Gut-brain axis

Accumulating evidence has shown that the densest flora niches in the human gut participate in regulating brain function and even host behavior. The two-way communication between the brain and intestinal flora, that is, the flora-gut-brain axis, operates predominantly through microbe-derived metabolites, vagus nerve, neuroimmune and neuroendocrine pathways. The afferent fibers of sympathetic and parasympathetic nerves link directly to the brain. Intestinal epithelial cells, including intestinal endocrine cells, keep close contact with the intestinal flora (*11,12*). For instance, metabolites of intestinal flora affect the secretion of satiety hormones by intestinal endocrine cells, such as glucagon-like peptide 1 (GLP-1), peptide YY (PYY), and cholecystokinin (CCK) (*12*). These hormones on the one hand activate the vagus nerve, transmit signals to the hypothalamus to control eating behavior, and on the other hand, enter the circulatory system to regulate eating behavior and other physiological processes. Studies in mice also showed that PYY and CCK could enhance feeding behavior (*13*).

To date, adequate shreds of evidence have shown that gut microbiota constitutes an important part of the gut-brain axis regulation. The main gut flora can be divided into five categories: *Bacteroidetes*, *Firmicutes*, *Verrucomicrobia*, *Proteobacteria*, and *Actinobacteria*. For healthy individuals, *Bacteroidetes* and *Firmicutes* are the main microbiota producing short-chain fatty acids (SCFAs) and occupy a major position in the gastrointestinal tract (GIT). SCFAs are one of the main bioactive metabolites produced in the gut (*14*). Acetate and propionate are mainly produced by *Bacteroidetes* phyla, whereas butyrate is mainly produced by *Firmicutes*. SCFAs influence lipid, glucose, and cholesterol metabolism in various tissues (*15*). Several clinical and preclinical studies indicate that SCFAs can regulate the release of satiety hormones in the GIT and manipulate the expression of anorectic neuropeptide (*e.g.*, proopiomelanocortin [POMC], neuropeptide Y [NPY], and agouti-related peptide [AgRP]) in the brain (*16-20*). Hunger and satiety signals initiate in the GIT and are delivered ascendingly into the hypothalamus.

Ghrelin, one of the "hunger hormones", is secreted in the GIT and bound to its receptor in the hypothalamus to regulate appetite. Leptin, another satiety hormone functionally opposite to ghrelin, also acts on its receptor in the hypothalamus to regulate energy consumption. Therefore, gut microbiota may be critical for maintaining metabolic homeostasis *via* the gut-brain axis regulation (*21)*.

4. Mechanisms of AIMD

4.1. AIMD and gut microbiota

Pre-clinic studies have found that traditional mice treated with OLZ and high-fat diet had more significant weight gain than those treated with high-fat diet only, but no significant difference was found in the same treatment of sterile mice (*22*). Transplanting feces from RIS-treated mice to traditional mice can cause significant weight gain and decrease in total resting metabolic rate compared to those without fecal transplantation (*23*). These preliminary findings suggest that gut microbiota is involved in the weight gain caused by antipsychotic drugs.

Antipsychotic treatment may cause alterations in the compositions of gut microbiota. It was found that the fecal abundance of *Actinobacteria* and *Proteobacteria* in patients receiving OLZ was decreased, accompanied by an increased *Firmicutes*/*Bacteroidetes* (*F/B*) ratio (*24*). An animal study in mice also found *Erysipelotrichi* (*Firmicutes* phylum) and *Gammaproteobacteria* (*Proteobacteria* phylum) was increased, and *Bacteroidia* (in *Bacteroidetes* phylum) was decreased in the OLZ-treated group. In addition, approximately 0.71% of body weight gain was accompanied by a 1% increase of abundance in *Erysipelotrichi*, indicating that *Erysipelotrichi* may mediate OLZ-induced weight gain (*22*). Bahr *et al*. compared flora composition, energy intake and consumption and weight between RIS-treated and placebo-treated female mice (*23*). They found that RIS treatment caused an increase in weight, together with alterations in the microbiome composition. The abundance of *Firmicutes* in RIS-treated mice increased by 32.6%, while the abundance of *Bateroidetes* decreased by 22.4%. Under *Firmicutes* phylum, compared with control mice, the abundance of *Lactobacillus* in mice treated with RIS was reduced, while *Allobaculum* was increased. Under *Bacteroidetes* phylum, RIS-treated mice had decreased *Alistipes* species and increased *Bacteroides* species (*23*). Flowers *et al*. also found that gut *Alistipes* was preferentially increased in patients with bipolar disorder or schizophrenia free from atypical antipsychotics (*25*). Interestingly, some studies found that AIMD could be alleviated by antibiotic treatment. The number of *Firmicutes* in the rats treated with antibiotics and OLZ was decreased and the number of Bacteroides increased, while the number of *Firmicutes* in rats treated with OLZ alone was increased and Bacteroides was decreased (*26*). These findings indicate that the increased abundance of *Firmicutes* and decreased abundance of *Bateroidetes* may help explain why SGAs can induce weight gain. Other clinical studies found that in patients treated with RIS, the weight, gut microbial diversity, *F/B* ratio, the abundance of *Escherichia coli* and *Bifidobacterium* were significantly increased, but the abundance of *Lactobacillus* and *Clostridium coccoides* group was decreased compared to that of the untreated group (*27,28*). Another study has found that the *Lachnospiraceae* abundance was increased, whereas the *Akkermansia* abundance was decreased in patients receiving SGAs (*29*). Studies of different age groups treated with RIS all reported an increase in the *F/B* ratio (*28-30*). Notably, a newly published animal study revealed that *Akkermansia muciniphila* could be a promising probiotic agent for alleviating systemic inflammation and OLZ-induced insulin resistance and hyperglycemia *via* regulation of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase - key enzymes in hepatic gluconeogenesis (*31*). Therefore, preclinical and clinical studies congruously observed the role of gut microbiota on AIMD, but its biological mechanism needs to be further elucidated.

4.2. AIMD and neurotransmitter receptors

SGAs act not only on dopamine receptors (DRs) in the brain but also on adrenergic α, cholinergic M1, histamine (H), and serotonin receptors. Through the comparison of blood glucose, DRs expression levels, and the weight between Roman high-avoidance or Roman low-avoidance mice treated with OLZ and traditional mice, Evers *et al*. found that only Roman high-avoidance mice showed a substantial increase in blood glucose, DRs expression, and weight (*30*), suggesting that AIMD may be associated with the expression of DRs. OLZ-induced weight gain and hyperphagia was blunted in serotonin 2C receptor (HTR_{2C}) knockout mice or treatment with the HTR2C-specific agonist (*32*). Another study found that in mice treated with OLZ, but not aripiprazole or haloperidol, showed a significant increase in weight and foraging behavior, while the binding density of the histamine receptor (HR) in the arcuate hypothalamic nucleus was decreased, suggesting that AIMD was also associated with H1 receptors *(33,34*).

White adipose tissue is now perceived as an endocrine organ that can release various peptides, such as adiponectin, leptin, resistin and visfatin, which are related to weight gain caused by SGAs. Elevated serum insulin levels were presented even in antipsychotic-free FEP patients, along with alterations in appetite regulating hormones, indicating predisposed metabolic dysfunction in FEP patients before antipsychotic treatment (*35*). Besides, SGAs also affect the expression of neuropeptides. OLZ treatment not only influenced body

weight, blood glucose level, and fatty acid community activity, but also up-regulated neuropeptide Y (NPY) mRNA expression and down-regulated POMC mRNA expression (*34*). Clinical studies have also found that AIMD is associated with the polymorphism of satiety-related hormone receptor genes. For example, one study reported that the blood leptin level was increased while ghrelin was decreased in AIMD patients (*36*). These findings indicate that several important neuropeptides are linked to AIMD.

Based on the above evidence, we speculate that, on the one hand, SGAs may affect the production of SCFAs in the intestine by changing the composition of intestinal flora. SCFAs mediate the secretion of PYY, GLP-1, CCK, and other peptides in intestinal endocrine cells, which activate the vagus nerve or transport through the blood-brain barrier (BBB), and regulate the expression of NPY receptors and POMC receptors in the hypothalamus, thus controlling foraging behavior. On the other hand, SGAs control foraging behavior by altering production of intestine-derived leptin and ghrelin and the expression of corresponding receptors in the brain. Summarized findings from animal and human studies related to mechanisms of AIMD in the gut-brain axis are listed in Table 1.

5. Metformin alleviates AIMD

Metformin, a biguanide component, is the first-line drug for type 2 diabetes. Metformin directly regulates the metabolism of glucose, promotes anaerobic fermentation of sugars, and increases absorption and utilization of glucose in peripheral tissues, such as muscle and fat. Besides, it can increase insulin sensitivity. Previous studies have shown that metformin can cause weight loss (*37*). An animal study found that metabolic dysfunction, including hyperglycemia, hyperlipidemia, insulin resistance, and white fat accumulation, was potently attenuated in rodents treated with both metformin and SGA compared with those with SGA only (*6*). Clinical studies also revealed that metformin combined with SGA could alleviate the problems of weight gain, body mass index (BMI) increase, hyperglycemia, and hyperlipidemia induced by SGA alone in pediatrics, adolescents, and adults as well, regardless of first-time treatment or retreatment (*38-40*). A systematic review and meta-analysis including 7 studies with 151 cases of antipsychotics plus metformin and 154 cases of antipsychotics plus placebo, found that weight and BMI were significantly reduced with the metformin supplement (*41*). Another meta-analysis on metformin for clozapine-associated obesity again found that in terms of weight loss (-3.12 kg, 95% CI: -4.88 kg to -1.37 kg) or BMI (-1.18 kg/m^2, 95%:CI: -1.76 kg/m^2 to -0.61 kg/m^2), metformin was overall superior to placebo (40). Similar results have been documented on metformin supplement in overweight patients with RIS treatment (*42*). Other meta-analytical evidence showed that in

Table 1. Animal and human studies related to mechanisms of AIMD in the gut-brain axis

Author, year	Drugs	Study subjects	Results	*Ref.*
Morgan, 2014	OLZ	Mouse	Traditional mice treated with OLZ and high-fat diet had more significant weight gain.	*22*
Bahr, 2015	RIS	Mouse	Weight gain and total resting metabolic rate decreased in mice that received fecal transplants from RIS-treated mice.	*23*
Davey, 2012	OLZ	Patient	*Actinobacteria* and *Proteobacteria* ↓, *F/B* ↑	*24*
Flowers, 2019	Antipsychotics	Patient	*Alistipes* ↓	*25*
Davey, 2013	OLZ	Rat	*Firmicutes* ↑ and *Bacteroidetes* ↓	*26*
Bahr, 2015	RIS	Female mouse	*Firmicutes* abundance (*Lactobacillus* species and *Allobaculum*) ↑, *Bateroidetes* abundance (*Bacteroides* species and *Alistipes* species) ↓	*23*
Bahr, 2015; Flowers, 2017	RIS	Patient	Weight ↑, Gut microbiota diversity ↑, *F/B* ↑, *Bifidobacterium* ↑, *Escherichia coli* ↑, *Clostridium coccoides* group and *Lactobacillus* ↓	*27* *28*
Yuan, 2018	RIS	Patient	*Lachnospiraceae* ↑, *Akkermansia* ↓	*29*
Evers, 2017	OLZ	Mouse	Roman high-avoidance mice showed increased body weight, blood glucose, and dopaminergic expression levels	*30*
Huang, 2021	OLZ	Mouse	*Akkermansia muciniphila* improves OLZ-related hyperglycemia and insulin resistance	*31*
Lord, 2017	OLZ	Mouse	AIMD was related to HTR_{2C}	*32*
Han, 2008	OLZ, RIS, ARI	Mouse	Weight and feeding behavior increased significantly in mice treated with OLZ or RIS, not ARI, while the binding density of the histamine receptor significantly decreased	*33*
Lian, 2014	OLZ, RIS, ARI	Rat	NPY mRNA expression ↑, POMC mRNA expression ↓	*34*
Potvin, 2015	Antipsychotics	Patient	Leptin ↑, ghrelin ↓	*36*

Abbreviations: OLZ, olanzapine; RIS, risperidone; ARI, aripiprazole; *F/B*, *Firmicutes*/*Bacteroidetesin*; AIMD, antipsychotic-induced metabolic dysfunction; HTR2C, serotonin 2C receptor; POMC, proopiomelanocortin; AMPK, AMP-activated protein kinase; NPY, Neuropeptide Y.

children and adolescents, whose weight was increased due to SGAs treatment, after 4, 12, or 16 weeks of continuous treatment with metformin, the weight of the metformin group was significantly reduced compared to placebo (*43*). Based on a rat model of schizophrenia established by consecutive injections of MK801 during the neurodevelopmental period, Luo *et al*. found that metformin attenuated OLZ- and RIS-induced metabolic dysfunctions in these rats without weakening the therapeutic effects of the antipsychotics (*44*). These clinical and pre-clinical findings together indicate the favorable outcome of metformin in managing AMID.

6. Mechanisms of metformin ameliorating AIMD

6.1. Metformin and gut microbiota

Previous studies have indicated that metformin plays its role in treating metabolic dysfunction possibly by changing the composition of gut microbiota. A study by Na-Ri Shin *et al*. showed that metformin could cause an increase in *Akkermansia* spp. population, indicating metfomin may regulate blood glucose *via* altering intestinal microbial composition (*45*). Meanwhile, Lee H *et al*. found that metformin treatment enriched *A. muciniphila in vitro*, which was in agreement with the results reported in *in vivo* mouse models. Therefore, metformin perhaps affects metabolic processes by increasing the *Akkermansia* spp. population (*46*). In addition, another study identified 22 enriched microbes and 24 depleted microbes in healthy mice treated with metformin. Within the class level, the relative abundances of *Prevotellaceae*, *Verrucomicrobiaceae*, *Rikenellaceae*, and *Porphyromonadaceae* were increased, while *Rhodobacteraceae* and *Lachnospiraceae* were decreased (47). Other clinical studies have also shown that metformin treatment could elevate the relative abundance of *Escherichia coli* (under phylum *Proteobacteria*) and reduce *Intestinibacter* (*48,49*), which was in line with findings from cross-sectional cohorts that compared untreated patients to metformin-treated patients with T2D (*50*). Pastor-Villaescusa *et al*. conducted a multicenter, double-blind, and randomized control trial including 160 obese children. It was found that metformin treatment resulted in a decrease in *Actinobacteria* abundance, while the *Bacteroidetes*, *Firmicutes*, and *Proteobacteria* abundances were different between the metformin and placebo treatment groups (*51*). Therefore, the effects of metformin on AMID may be associated with alterations in gut microbial composition.

6.2. Metformin acts on the brain

Existing evidence indicates that metformin may cross the BBB to act on the brain and directly influence the central nervous system (*52*). Hypothalamic AMP-activated protein kinase (AMPK) is a dominant adjustment factor of food intake, and preclinical studies found that metformin could act on cultured hypothalamic neurons *via* blocking the increase of AMPK phosphorylation and NPY expression, and thus decrease glucose levels (*53-55*). Meanwhile, intracerebroventricular injection of metformin promoted POMC expression and induced anorexia in a rat model (*56*). The hypothalamic phosphorylated signal transducer and activator of transcription 3 (pSTAT3) signaling to the central mechanisms are critical for regulating energy intake and consumption. A previous study showed that a decrease in hypothalamic STAT3 signaling initiated weight gain by hyperphagia and adiposity with changes in glucose homeostasis (*57*). A Lee *et al*. study suggested that metformin could directly act on the hypothalamus and cause an increase in pSTAT3 expression, and changes in POMC mRNA had a similar tendency with pSTAT3, eventually inducing an anorexic status (*56*). Moreover, metformin could down-regulate expression of AgRP mRNA, an orexigenic neuropeptide mainly expressed in the arcuate neurons that robustly stimulates food intake (*58,59*).

In addition, metformin also affects the expression of hypothalamic neurotransmitters. Some researchers have observed that metformin could play a selective 5-HT receptor activator-like role in mouse neuroblastoma N1E-115 cells, and activate the 5-HT3 receptor to regulate gastrointestinal motility. Additionally, metformin can increase the expression of receptors in the hypothalamus to improve individual sensitivity to leptin and insulin, thus playing an anorexic role (*60*). Detailed findings in studies investigating the mechanisms of metformin on AMID *via* the gut-brain axis are listed in Table 2.

7. Conclusion

In summary, accumulating studies have proved that both AIMD and metformin are closely related to the gut-brain axis (Figure 1). SGAs act on the GIT to alter the composition and metabolism of gut microbiota, mainly causing an increase in *F/B* ratio, and a decrease in *Proteobacteria* and *Akkermansia*. Interestingly, metformin plays an opposite role by increasing the abundance of *Akkermansia*. Changes in microbiota composition consequently caused changes in SCFA production and other microbe-derived metabolites. SGAs also act on various receptors and regulate neuropeptides in the hypothalamus, including up-regulation of NPY, AgRP mRNA expression, and down-regulation of POMC expression, while metformin can down-regulate the expression of NPY, AgRP mRNA and up-regulate POMC expression, and block the activation of hypothalamic AMPK signaling, thus coordinating the gut-brain axis to regulate the balance between leptin and ghrelin to maintain metabolic homeostasis and foraging behavior. In conclusion, metformin may be a promising agent for controlling AIMD. More well-

Table 2. Multiple mechanisms of metformin ameliorating AIMD via the gut-brain axis

Author, year	Study subjects	Results	*Ref.*
Na-Ri, 2019	Mouse	*Akkermansia* spp ↑	*45*
Lee, 2014	Mouse	*Akkermansia* spp. (*A.muciniphila*) ↑	*46*
Ma, 2018	Mouse	Healthy mice treated with metformin showed 46 significantly changed microbes, including 22 enriched and 24 depleted microbes identified within the class level Prevotellaceae, *Porphyromonadaceae*, *Verrucomicrobiaceae*, *Rikenellaceae* ↑ and *Lachnospiraceae*, *Rhodobacteraceae* ↓	*47*
Elbere, 2018; Forslund, 2015	Patient	*Escherichia coli* ↑, *Intestinibacter* ↓	*48, 49*
Mirshamsi, 2004	Rat, mouse	NPY expression ↓, pSTAT3 ↓	*57*
Lee, 2012	Rat	pSTAT3 ↑, POMC ↓	*56*
Cubeddu, 2000; Bing, 2006	Patient	AgRP mRNA ↓	*58 59*
Auber, 2011	Rat	5-HT receptor, leptin receptor ↑	*60*

Abbreviations: SCFAs, short-chain fatty acids; AMPK, AMP-activated protein kinase; NPY, neuropeptide Y; POMC, proopiomelanocortin; AgRP, agouti-related peptide; pSTAT3, phosphorylated signal transducer and activator of transcription 3; 5-HT, 5-hydroxytryptamine.

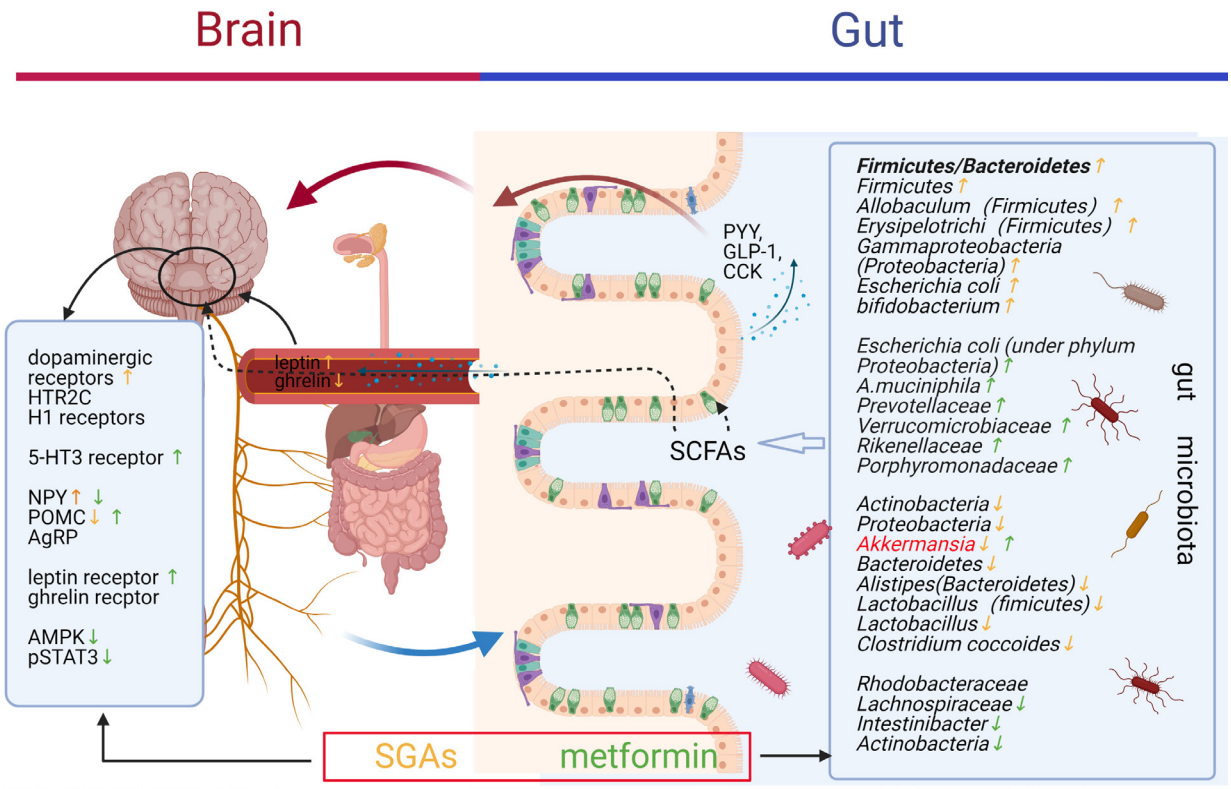

Figure 1. The mechanisms of AIMD and metformin ameliorating AIMD. SGAs act on GIT to alter the composition and metabolism of gut microbiota (marked by an orange arrow). Metformin plays an opposite role on *Akkermansia* (marked with red; both SGAs and metformin alter its abundance), and also influences the abundances of other microbes (marked by a green arrow). Changes in microbiota composition consequently cause changes in SCFAs production. SCFAs act on the intestinal endocrine cell to regulate the secretion of PYY, GLP-1, and CCK, which subsequently activate the vagus nerve to send signals to the brain. SGAs also acts on various receptors and regulate neuropeptides in the hypothalamus (marked by an orange arrow), while metformin can down-regulate the expression of NPY, AgRP mRNA and up-regulate POMC expression, and inhibit hypothalamic AMPK signals (marked by a green arrow). Other receptors are also related to the development of AIMD and metformin treatment, but the detailed correlation is still unclear (not marked by any arrow). Therefore, metformin coordinates the gut-brain axis to regulate the balance between leptin and ghrelin to maintain metabolic homeostasis and modulate foraging behavior.

designed clinical trials on this topic are warranted.

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